Pergamon

Tetrahedron 58 (2002) 10167–10171

TETRAHEDRON

Addition of organolithium reagents to Ahc methyl ester. An approach to new α-amino ketones

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Received 22 April 2002; revised 1 August 2002; accepted 24 October 2002

Abstract—We have developed a versatile methodology to obtain α-amino ketones by acylation of methyl *N*-benzoyl-7-azabicyclo[2.2.1]-heptane-1-carboxylate (**1**) with organolithium reagents. The reaction proceeds via a stable tetrahedral intermediate. When methyl ester **1** was treated under the same conditions but with a different work up procedure (careful addition of saturated NH_4Cl), we observed by ^1H NMR spectroscopy that a new compound had appeared in the crude reaction mixture corresponding to a hemiacetal.

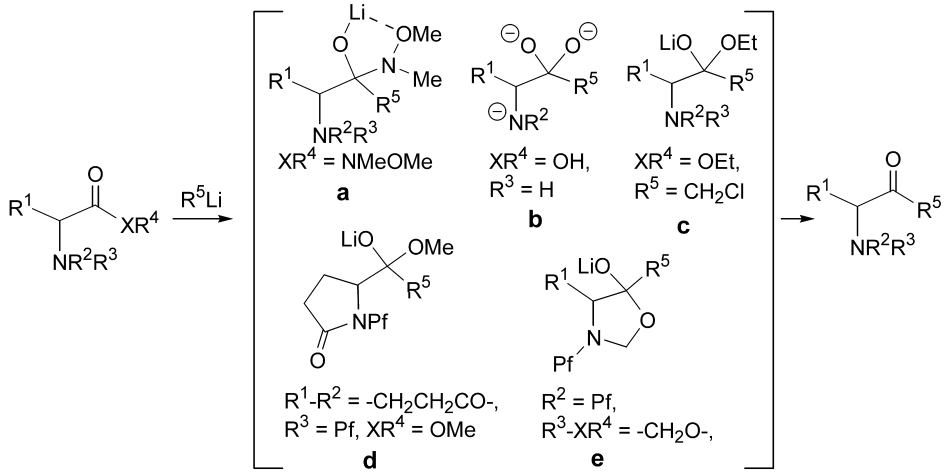
1. Introduction

Recently, the synthesis of *N*-protected α-amino ketones has attracted the attention of numerous research groups. These substrates are important starting materials in the synthesis of interesting biologically active compounds.[1–4]

Several synthetic routes have been developed to gain access to these systems and, among these routes, the reaction of *N*-protected α-amino acids, esters or amides with organolithium or Grignard reagents is a valuable approach.[5] One problem associated with this procedure is the occurrence of nucleophilic addition to the ketone of an organometallic molecule to generate a tertiary alcohol. In order to prevent this problem, stabilization of the tetrahedral alkoxide intermediate is essential.

In Scheme 1 we outline the few methods by which it is possible to obtain the desired product, by means of stabilization of the intermediates **a**–**e**, formed in the organometallic addition with *N*-methoxy-*N*-methylamides[6,7] (**a**), lithium carboxylates[8,9] (**b**), α-polyhaloesters[10] (**c**), cyclic amido esters[11] (**d**) or *N*-(9-phenylfluoren-9-yl)-amino acid-derived oxazolidinones[12,13] (**e**).

Of all the amino ketones, especially given their extensive



Scheme 1. Organolithium acylations with α-amino acids, esters or amides and their stable intermediates **a**–**e**.

Keywords: bicyclic heterocyclic compounds; acylation; amino acids and derivatives; amino ketones; lithium and compounds.

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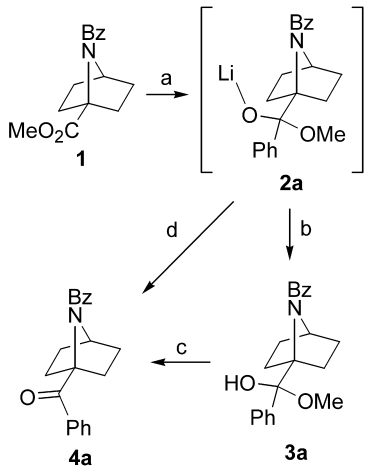


Scheme 2. (a) PhBr, *n*-BuLi, THF, −78°C; (b) NH_4Cl, −78°C→rt; (c) silica gel; (d) 0.5N HCl, −78°C→rt.

synthetic use, proline derivatives have received special attention in this area. For example, (*S*)-2-acetylpyrrolidine has been used in the synthesis of several alkaloids.[14–17]

2. Results and discussion

We have substantial experience in the field of amino acid research and, in particular, in the area of restricted α-amino acids.[18–20] In this context we have recently synthesised 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (Ahc)—a type of constrained proline[21]—and have developed a versatile route to obtain azabicycle derivatives with substituents in position 1.[22] We report here the organolithium acylation of methyl *N*-benzoyl-7-azabicyclo[2.2.1]-heptane-1-carboxylate (**1**), a precursor of Ahc. This protected amino acid is achiral and, therefore, problems arising from racemization during the additions with organometallics will not be an issue and achiral ketones or alcohols are obtained in all cases.

Initially, we attempted the acylation of phenyllithium with compound **1**, as shown in Scheme 2. According to the literature,[11–13] an excess of the organolithium reagent (1.5 equiv.) is required to obtain good yields of ketone and avoid the formation of the tertiary alcohol. Under these conditions, and using THF as the solvent at −78°C, we obtained an 8:2 ratio of ester **1** to ketone **4a** and traces of alcohol were not observed.

In order to increase the yield of the acylation we used more equivalents of the organolithium reagent (3 equiv.) and, after 2 h reaction time, we carried out the work up procedure with 0.5N HCl. The ^{1}H NMR spectrum of the crude reaction mixture contained the signals due to ketone **4a**, a small amount of the starting material and no evidence for the alcohol. Further purification by silica gel column chromatography furnished the ketone **4a** in 86% yield (Scheme 2).

However, when methyl ester **1** was treated under the same conditions, albeit with a different work up procedure (careful addition of saturated NH_4Cl), ^{1}H NMR spectroscopy showed the presence in the crude reaction mixture of a small amount of ketone **4a** and a large amount of a new

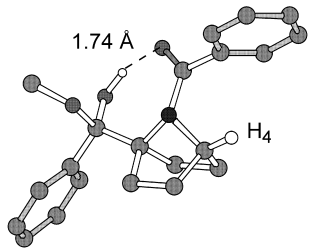


Figure 1. Conformer of minimum energy of hemiacetal **3a**.

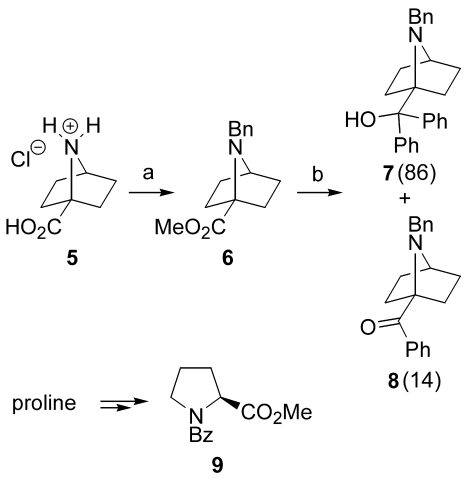
compound, identified as the hemiacetal **3a**. In the ^{1}H NMR spectrum the signals of the OMe and OH protons can be observed at 3.27 and 9.21 ppm, respectively. The OH signal is shifted to very low fields due to hydrogen bonding with the carbonyl group of the benzamide group, as shown in Fig. 1.

Additional investigations into the seven-membered hydrogen bonded ring were carried out by several types of calculation. First, the conformational analysis of compound **3a** was developed by semiempirical calculations (PM3) and the conformer of minimun energy was re-optimized with ab initio calculations, carried out with the Gaussian-98 program[23] using HF/6-31G*. Fig. 1 shows one stereoview of the conformation of minimum energy (−‴ 1087.230328 hartree) with hydrogen bonding (1.74 Å). A relevant feature is observed in this structure; the disposition of the benzene ring of the benzamide group at a 119° angle with respect to the carbonyl group, which results from the steric impediment with H_4 of the bicycle. This feature had already been observed in this kind of bicycle in the solid state.[22]

In an attempt to purify this compound by silica gel column chromatography, it was found that the mildly acidic medium is sufficient to transform hemiacetal **3a** into ketone **4a**. On the basis of this evidence, and in agreement with the literature,[11,12,24,25] we propose the involvement of a stable tetrahedral intermediate **2a** (Scheme 2). The stabilization could be due to the interaction between the lithium and the oxygen of the benzamide group, in a similar way to that described for the addition of organolithium reagents to *N*-methoxy-*N*-methylamides (intermediate **a** in Scheme 1). In the case reported here, however, a seven-membered ring is formed rather than a five-membered one.

With the purpose of evaluating the influence of the carbonyl group of the benzamide, we attempted the addition of the organometallic reagent to methyl *N*-benzyl-7-azabicyclo-[2.2.1]heptane-1-carboxylate **6**. This compound was obtained by esterification and benzylation of the Ahc hydrochloride derivative **5**, which is prepared by acid hydrolysis of compound **1**.[21] The reaction of amino ester **6** with PhLi gave a mixture of tertiary alcohol and ketone in an 86:14 ratio in favour of the alcohol, as determined by ^{1}H NMR spectroscopy (Scheme 3).

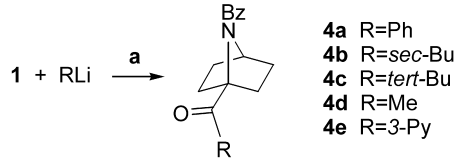
With these results in mind, and in order to verify the effect that the conformationally constrained system has on this reaction, the proline derivative **9** was treated under several sets of conditions with PhLi. In each case we obtained a complex mixture in which the corresponding ketone could



Scheme 3. (a) (i) AcCl, MeOH, (ii) BnBr, DIEA; (b) PhLi, THF, −78°C.

Table 1. Addition of organolithium nucleophile to ester **1**

Entry	R	Equivalents	Work up	Compound (yield)
1	Ph	1.5	HCl	**4a** (20)
2	Ph	3	NH_4Cl	**3a** (82)
3	Ph	3	HCl	**4a** (97)
4	*sec*-Bu	3	HCl	**4b** (51)
5	*tert*-Bu	3	HCl	**4c** (99)
6	Me	3	HCl	**4d** (99)
7	3-Py	3	HCl	**4e** (81)



Scheme 4. (a) THF, −78°C.

be detected by ESI-MS as a minor subproduct. This situation implies significant influence of the benzamide group and the quaternary centre on the stability of intermediate **2a**.

We extended this methodology to include other organolithium reagents such as MeLi, *sec*-BuLi, and *tert*-BuLi, obtaining moderate to excellent yields (Scheme 4). The results are shown in Table 1.

In order to investigate the scope of this reaction, we attempted the acylation of heterocyclic compounds. For example, 3-lithiumpyridine was obtained in situ from 3-bromopyridine and the acylation was carried out according to the standard procedure, obtaining the ketone **4e**. Indeed, this methodology has the versatility to provide other attractive compounds (Scheme 4).

3. Conclusions

In conclusion, we have developed a versatile methodology to obtain α-amino ketones by acylation of organolithium reagents with methyl *N*-benzoyl-7-azabicyclo[2.2.1]-heptane-1-carboxylate via a stable tetrahedral intermediate. Synthesis of epibatidine analogues and enantiomerically pure amino alcohols incorporating the 7-azabicyclo skeleton, using this methodology, is currently in progress.

4. Experimental

4.1. General procedure

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in CD_3OD with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 1000 spectrometer. Mass spectra were obtained by electrospray ionization (ESI).

4.2. General procedure for acylation with organolithium reagents

Method A. To a precooled solution of **1** (1 equiv.) in THF (10 mL) at −78°C was added dropwise the organolithium reagent (3 equiv.) in THF over 5 min. The resultant yellow solution was stirred for an additional 2 h at −78°C. The reaction mixture was quenched with 5 mL of 0.5N HCl. The aqueous layer was extracted with ethyl acetate (2×10 mL) and the organic layer was washed with brine (10 mL), dried (anhydrous Na_2SO_4) and concentrated to give the ketones **4b**, **4c** and **4d**.

Method B. To a precooled solution of PhBr or 3-BrPy (1 equiv.) in THF (5 mL) at −78°C was added dropwise *n*-BuLi (1.1 equiv., 0.55 mL of a 2 M solution in cyclohexane) over 5 min. The reaction mixture was stirred for 30 min at the same temperature and a solution of ester **1** (0.3 equiv.) in THF (5 mL) was added. The resultant yellow solution was stirred for an additional 2 h at −78°C. The reaction mixture was quenched with 5 mL of 0.5N HCl (5 mL of saturated NH_4Cl to obtain **3a**). The aqueous layer was extracted with ethyl acetate (2×10 mL) and the organic layer was washed with brine (10 mL), dried (anhydrous Na_2SO_4) and concentrated to give the ketones **4a** and **4e**.

4.2.1. (*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)methoxyphenylmethanol (3a). 90% yield as a colourless oil. ^1H NMR ($CDCl_3$): δ 1.19–1.38 (m, 4H); 1.61–1.68 (m, 1H); 1.95–2.02 (m, 1H); 2.30–2.45 (m, 1H); 2.50–2.62 (m, 1H); 3.27 (s, 3H, CH_3O); 4.12–4.18 (m, 1H, H_4); 7.30–7.72 (m, 10H, Arom.); 9.21 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 27.7, 30.2, 30.4, 33.6, 49.1, 62.9, 77.4, 98.7, 127.6, 127.7, 128.1, 128.2, 129.9, 130.6, 136.7, 140.0, 169.2.

4.2.2. (*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)phenylketone (4a). The residue was chromatographed on a silica gel column, eluting with hexane/ethyl acetate (7:3), to yield 97% of compound **4a** as white solid. Mp: 155–157°C. ESI+(*m*/*z*)=306.5. Anal. calcd for $C_{20}H_{19}NO_2$; C, 78.66; H, 6.27; N, 4.59; found C, 78.98; H, 6.15; N, 4.71. ^{1}H NMR ($CDCl_3$): δ 1.60–1.72 (m, 2H); 1.86–2.20 (m, 4H); 2.42–2.58 (m, 2H); 4.40–4.47 (m, 1H, H_4); 7.35–7.50 (m, 6H, Arom.); 7.64–7.72 (m, 2H, Arom.); 8.20–8.27 (m, 2H, Arom.). ^{13}C NMR ($CDCl_3$): δ 30.0, 32.7 (C_2, C_3, C_5, C_6); 62.7 (C_4); 73.0 (C_1); 128.1, 128.2, 128.3, 128.4, 131.5, 132.3, 134.6, 135.7 (Arom.); 172.9 (CON); 196.1 (CO).

4.2.3. 1-(*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)-*sec*-butylketone (4b). The residue was chromatographed on a silica gel column, eluting with hexane/ethyl acetate (6:4), to yield 51% of compound **4b** as a colourless oil. ESI+(*m*/*z*)=286.6. Anal. calcd for $C_{18}H_{23}NO_2$; C, 75.76; H, 8.12; N, 4.91; found C, 75.57; H, 8.01; N, 4.85. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3H, *J*=7.5 Hz); 1.19 (d, 3H, *J*=6.6 Hz); 1.30–1.62 (m, 3H); 1.66–2.05 (m, 5H); 2.30–2.41 (m, 2H); 2.86–2.96 (m, 1H); 4.20–4.27 (m, 1H, H_4); 7.36–7.50 (m, 3H, Arom.); 7.64–7.71 (m, 2H, Arom.). ^{13}C NMR ($CDCl_3$): δ 11.6, 16.7, 26.9, 30.5, 30.6, 31.5, 31.9, 43.8 ($2CH_3$, CH, CH_2, C_2, C_3, C_5, C_6); 62.2 (C_4); 73.2 (C_1); 128.3, 128.5, 131.4, 134.7 (Arom.); 173.0 (CON); 211.3 (CO).

4.2.4. 1-(*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)-*tert*-butylketone (4c). The residue was chromatographed on a silica gel column, eluting with hexane/ethyl acetate (8:2), to yield 99% of compound **4c** as white solid. Mp: 150–154°C. ESI+(*m*/*z*)=286.6. Anal. calcd for $C_{18}H_{23}NO_2$; C, 75.76; H, 8.12; N, 4.91; found C, 75.94; H, 8.23; N, 4.83. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9H); 1.49–1.56 (m, 2H); 1.65–2.08 (m, 4H); 2.30–2.47 (m, 2H); 4.21–4.28 (m, 1H, H_4); 7.35–7.50 (m, 3H, Arom.); 7.58–7.65 (m, 2H, Arom.). ^{13}C NMR ($CDCl_3$): δ 28.2 [C(*C*H_3)$_3$]; 29.9, 32.1 (C_2, C_3, C_5, C_6); 44.6 [*C*(CH_3)$_3$]; 61.9 (C_4); 73.3 (C_1); 128.1, 128.4, 131.3, 134.9 (Arom.); 173.3 (CON); 212.0 (CO).

4.2.5. 1-(*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)-methylketone (4d). The residue was chromatographed on a silica gel column, eluting with hexane/ethyl acetate (8:2), to yield 99% of compound **4d** as a solid. Mp: 143–145°C. ESI+(*m*/*z*)=244.3. Anal. calcd for $C_{15}H_{17}NO_2$; C, 74.05; H, 7.04; N, 5.76; found C, 73.89; H, 7.18; N, 5.66. ^{1}H NMR ($CDCl_3$): δ 1.52–1.62 (m, 2H); 1.64–1.77 (m, 2H); 1.88–1.94 (m, 2H); 2.13–2.25 (m, 2H); 2.30 (s, 3H); 4.22–4.31 (m, 1H, H_4); 7.35–7.50 (m, 3H, Arom.); 7.62–7.70 (m, 2H, Arom.). ^{13}C NMR ($CDCl_3$): δ 25.6 (CH_3); 30.5, 30.9 (C_2, C_3, C_5, C_6); 62.3 (C_4); 73.8 (C_1); 128.3, 128.4, 131.5, 134.5 (Arom.); 173.0 (CON); 205.0 (CO).

4.2.6. (*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)pyridin-3-ylketone (4e). The residue was chromatographed on a silica gel column, eluting with hexane/ethyl acetate (8:2), to give 81% of compound **4e** as an oil. ESI+(*m*/*z*)=307.3. Anal. calcd for $C_{19}H_{18}N_2O_2$; C, 74.49; H, 5.92; N, 9.14; found C, 74.29; H, 5.84; N, 9.26. ^{1}H NMR ($CDCl_3$): δ 1.66–1.73 (m, 2H); 1.85–2.10 (m, 4H); 2.47–2.55 (m, 2H); 4.42–4.50 (m, 1H, H_4); 7.32–7.54 (m, 4H, Arom.); 7.62–7.70 (m, 2H, Arom.); 8.42–8.50 (m, 1H, Arom.); 8.63–8.69 (m, 1H, Arom.); 9.49 (s, 1H, Arom.). ^{13}C NMR ($CDCl_3$): δ 30.1 (C_2, C_3, C_5, C_6); 62.7 (C_4); 73.1 (C_1); 123.6, 128.3, 128.4, 131.8, 135.8 142.2, 149.4, 152.6, 159.9 (Arom.); 194.9 (CO).

4.2.7. Methyl *N*-benzyl-7-azabicyclo[2.2.1]heptane-1-carboxylate (6). Acetyl chloride (107 μL, 1.5 mmol) was added dropwise to methanol (10 mL) at 0°C. The mixture was stirred for 10 min and amino acid hydrochloride **5** (200 mg, 1.03 mmol) was added. The resulting solution was stirred at 60°C for 12 h. The solvent was removed, the residual oil suspended in diethyl ether (20 mL) and the solvent evaporated again. The solvent addition/evaporation was repeated twice more and the methyl ester was obtained as a pure, colourless oil. ^{1}H NMR (CD_3OD) δ 1.79–1.86 (m, 2H); 2.05–2.13 (m, 6H); 4.16–4.20 (m, 1H, H_4); 3.79 (s, 3H, CO_2CH_3); ^{13}C NMR (CD_3OD) δ 30.7, 31.6 (C_2, C_3, C_5, C_6); 55.8, 62.7 (CO_2CH_3, C_4); 74.8 (C_1); 172.1 (CO_2CH_3). The methyl ester hydrochloride was dissolved in dry acetonitrile (25 mL) under an argon atmosphere and BnBr (178 μL, 1.5 mmol) and DIEA (434 μL, 2.5 mmol) were added to the mixture. The reaction mixture was stirred at 50°C for 24 h. The solvent was removed and the residual solid was dissolved in CH_2Cl_2. The resulting suspension was washed with saturated aqueous $NaHCO_3$ (2×30 mL) and brine (30 mL), dried and the solvent was evaporated to give an oil, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **6** (96 mg, 78%) as a colourless oil. ESI+(*m*/*z*)=246.6. Anal. calcd for $C_{15}H_{19}NO_2$; C, 73.44; H, 7.81; N, 5.71; found C, 73.61; H, 7.74; N, 5.82. ^{1}H NMR ($CDCl_3$): δ 1.33–1.45 (m, 2H); 1.66–1.79 (m, 2H); 1.84–1.96 (m, 2H); 2.09–2.19 (m, 2H); 3.24–3.32 (m, 1H, H_4); 3.56 (br s, 2H, CH_2Ph); 3.68 (s, 3H, CO_2CH_3); 7.21–7.41 (m, 5H, Arom.). ^{13}C NMR ($CDCl_3$): δ 28.0, 32.7 (C_2, C_3, C_5, C_6); 50.2, 51.8, 59.6 (CH_2Ph, CO_2CH_3, C_4); 71.0 (C_1); 126.7, 128.1, 128.8, 139.6 (Arom.); 173.6 (CO_2CH_3).

4.2.8. (*N*-Benzyl-7-azabicyclo[2.2.1]hept-1-yl)-diphenylmethanol (7) and (*N*-benzyl-7-azabicyclo[2.2.1]hept-1-yl)-phenylketone (8). The reaction was carried out following the general procedure (Method B) for acylation of the organolithium. The mixture was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **7** as an oil and **8** as a mixture with compound **7**. Data for compound **7**: ESI+(*m*/*z*)=370.5. Anal. calcd for $C_{26}H_{27}NO$; C, 84.51; H, 7.37; N, 3.79; found C, 84.72; H, 7.23; N, 3.68. ^{1}H NMR ($CDCl_3$): δ 1.22–1.44 (m, 4H); 1.78–1.86 (m, 2H); 2.30–2.42 (m, 2H); 3.10–3.17 (m, 1H, H_4); 3.58 (br s, 2H, CH_2Ph); 7.16–7.34 (m, 12H, Arom.); 7.74–7.80 (m, 3H, Arom.). ^{13}C NMR ($CDCl_3$): δ 28.1, 32.3 (C_2, C_3, C_5, C_6); 50.1, 58.8 (CH_2Ph, C_4); 74.7, 79.6 (COH, C_1); 126.6, 126.7, 127.5, 128.0, 128.1, 128.2, 128.6, 129.9, 140.4, 147.1 (Arom.). Extracted data for compound **8** from the mixture of **7** and **8**: ESI+(*m*/*z*)=292.4. Signal of ketone ^{13}C NMR ($CDCl_3$): δ 201.5 (CO).

4.2.9. Methyl *N*-benzoylpyrrolidine-2-carboxylate (9). Acetyl chloride (558 μL, 7.8 mmol) was added dropwise to methanol (10 mL) at 0°C. The mixture was stirred for 10 min and the proline (300 mg, 2.6 mmol) was added. The resulting solution was stirred at 60°C for 12 h. The solvent was removed, the residual oil suspended in diethyl ether (20 mL) and the solvent evaporated again. The solvent

addition/evaporation was repeated twice more and methyl ester was obtained as a pure, white solid. Mp: 80–84°C. ^{1}H NMR (CD_3OD) δ 1.94–2.10 (m, 3H); 2.30–2.40 (m, 1H); 3.27–3.37 (m, 2H); 3.77 (s, 3H, CO_2CH_3); 4.34–4.40 (m, 1H, H_2). ^{13}C NMR (CD_3OD) δ 27.0, 31.8, 49.7, 56.4, 63.2 (C_2, C_3, C_4, C_5, CO_2CH_3); 173.0 (CO_2CH_3). The methyl ester hydrochloride was dissolved in dry CH_2Cl_2 (25 mL) under an argon atmosphere and BzCl (604 μL, 5.2 mmol) and DIEA (1.35 mL, 7.8 mmol) were added. The mixture was stirred at 50°C for 24 h. The solvent was removed and the residual solid dissolved in CH_2Cl_2. The resulting suspension was washed with saturated aqueous $NaHCO_3$ (2×30 mL) and brine (30 mL), dried and the solvent was evaporated to give an oil, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **9** (512 mg, 85%) as a colourless oil. ESI+(m/z=234.0. Anal. calcd for $C_{13}H_{15}NO_3$; C, 66.94; H, 6.48; N, 6.00; found C, 67.11; H, 6.36; N, 6.12. ^{1}H NMR ($CDCl_3$): δ 1.72–1.96 (m, 3H); 2.16–2.25 (m, 1H); 3.38–3.57 (m, 2H); 3.67 (s, 3H, CO_2CH_3); 4.56 (dd, 1H, J=8.4, 5.1 Hz, H_2), 7.24–7.35 (m, 3H, Arom.); 7.43–7.51 (m, 2H, Arom.). ^{13}C NMR ($CDCl_3$): δ 25.4, 29.4, 49.9, 52.2, 59.1 (C_2, C_3, C_4, C_5, CO_2CH_3); 127.3, 128.2, 130.2, 136.2 (Arom.); 169.7, 172.8 (CON, CO_2CH_3).

Acknowledgements

We thank the Comision Interministerial de Ciencia y Tecnología (CICYT) and the Comisión Europea (project 2FD97-1530), the Gobierno de La Rioja (ANGI-2001/30) and the Universidad de La Rioja (project API-01/B02).

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